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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Fowlkes et al.

Confirmation No.: 4623

Serial No.: 09/286,166

Group Art Unit: 1646

Filed: April 5, 1999

Examiner: Michael T. Brannock

For: YEAST CELLS ENGINEERED TO PRODUCE PHEROMONE SYSTEM PROTEIN SURROGATES, AND USES THEREFOR

Atty Docket No.: 11072-009 (formerly CPI-012CP4BCN)

SUBMISSION UNDER 37 C.F.R. §1.114

Assistant Commissioner for Patents
Box AF
Washington, D.C. 20231

Sir:

In response to the Final Office Action mailed December 14, 2001 and in accordance with Rule 116 of the Rules of Practice, please enter the following remarks. Applicants submit herewith: (1) Power of Attorney by Assignee of Entire Interest and Revocation of Prior Power of Attorney; (2) Transmittal of Power of Attorney and Revocation; (3) a Request for Corrected Filing Receipt; (4) a Petition For Extension of Time (in duplicate) for a period of three months, from March 14, 2002 up to and including June 14, 2002, accompanied by the appropriate fee; (5) a Request for Continued Examination, accompanied by the appropriate fee; and (6) Exhibit A: a copy of the claims that will be pending upon entry of the instant amendment.

REMARKS

Claims 43 to 58 are pending in the instant application. Applicants request continued examination of the instant application by considering the following remarks.

I. THE OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

Applicants intend to address this rejection upon an indication that the application is otherwise allowable.

II. THE REJECTION UNDER 35 U.S.C. §103 (a) SHOULD BE WITHDRAWN

Claims 43, 44, 45, 47, 50, 51, 52, 54, 55, 57, and 58 are rejected under 35 U.S.C. § 103 (a) as being obvious over the U.S. Patent No.5,284,746 issued February 4, 1994 to Sledziewski et al. ("Sledziewski") in view of Kang *et al.*, Mol. Cell Biol., 1990, 10:2582-2590 ("Kang"). According to the Examiner, Sledziewski discloses a transformed yeast cell comprising a reporter gene under control of a pheromone-responsive promoter and a heterologous G-protein coupled receptor gene under a separate promoter, wherein said receptor is a hybrid receptor comprising intracellular sequences from yeast and sequences from heterologous receptors, wherein said yeast receptor sequences are STE2 sequences, wherein said receptors are capable of inducing yeast pheromone response, and a mutation in the *ste2* gene causing increased sensitivity to receptor activation. According to the Examiner, Kang discloses a heterologous yeast/mammalian hybrid Gα protein expressed in yeast that complements the cell cycle arrest in cells lacking endogenous Gα. According to the Examiner, although Sledziewski does not teach a hybrid Gα protein, it would be obvious to one of ordinary skill in the art, in view of Kang, to use the hybrid G-protein receptors in the Sledjiewski assay. Applicants respectfully disagree for the following reasons.

A. The Claimed Invention

The present invention relates to a transformed yeast cell useful in cell-based screening assays in yeast. The transformed cell has a heterologous G protein-coupled receptor gene and a reporter gene under control of a pheromone-responsive promoter, each under the control of a separate promoter, a mutation in a SCG1/GPA1 gene, and a hybrid Gα protein. The invention is based, in part, on the discovery by the Applicants of yeast strains in which heterologous G protein-coupled receptors are linked to the pheromone response pathway.

This link between the heterologous receptor and the downstream effectors of the pathway is made possible via hybrid G proteins, which have sequences in common with both yeast and heterologous Gα proteins, allowing them to interact with a heterologous receptor on the one hand, and a yeast Gβγ protein on the other. The hybrid Gα proteins, once activated by the receptor, in turn activate downstream pheromone pathway effectors. Activity is monitored using a reporter gene under control of a pheromone-responsive promoter. Such yeast cells are useful in screening assays for drugs capable of modulating in the pheromone signal transduction pathway of yeast and other G-protein coupled receptor pathways.

The art relied on by the Examiner does not disclose or even suggest the claimed transformed yeast cells as is set forth in detail below.

B. The Legal Standard To Establish A Prima Facie Case of Obviousness

A finding of obviousness under 35 U.S.C. §103 requires a determination of: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the difference between the claimed subject mater and the prior art; and (4) whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1966).

First, the relevant inquiry is: (1) whether the prior art suggests the invention; and (2) whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Second, the Federal Circuit has stated time and again that one cannot consider a reference in less than the entirety, *i.e.*, disregard disclosures in the reference that diverge from and teach away from the invention. Specifically, the Federal Circuit, stated, "It is impermissible within the framework of a Section 103 rejection to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the reference fairly suggests to one of ordinary skill in the art". *In re Wesslau*, 353 F.2d 238, 241 (CPCA 1965).

Third, the Federal Circuit has also held that the prior art must either expressly disclose every claim limitation or suggest modifications to meet every claim limitation. *Litton Indus. Products, Inc. v. Solid State Systems*, 755 F.2d 158, 164 (Fed. Cir. 1985). In *Litton*, the

District Court found that a device was obvious by focusing on what "it thought was the 'most critical feature.'" The Federal Circuit reversed this decision because the cited references neither taught specific claim elements nor suggested to one of ordinary skill in the art the necessary modifications. *See also, Gore & Assoc. v. Garlock Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (holding restriction of multi-step process to one step to invalidate claims constitutes error even when prior art shows one step in a process otherwise distinct).

Finally, the Federal Circuit has also stated time and again that for the disclosures of two or more prior art references to be combined in order to establish *prima facie* obviousness "[t]here must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." *In re Jones*, 21 USPQ2d 1941, 1943-1944 (Fed. Cir. 1992); *In re Fine*, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988) (Emphasis added). Moreover, the Federal Circuit has made very clear that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, at 1075. A single concept in a prior art reference should not be taken out of context and relied upon with the benefit of hindsight to show obviousness in a multi-step process never before done or disclosed. Instead, a reference must be considered as a whole. *Panduit v. Dennison Mfg. Co.*, 227 U.S.P.Q. 337, 344 (Fed. Cir. 1985).

C. Sledjiewski And Kang, Whether Considered Individually Or In Combination, Do Not Teach or Suggest The Claimed Invention

The combination of Sledjiewski and Kang does not suggest the required elements of the transformed yeast cells covered by the claims, *i.e.*, a reporter gene under control of a pheromone-responsive promoter, a heterologous G protein-coupled receptor gene, each said gene being under the control of a separate promoter, a mutation in a SCG1/GPA1 gene, and a hybrid Gα protein. Therefore, the invention, as claimed, cannot be obvious.

1. The Teachings of Sledjiewsky

Sledjiewski teaches a yeast cell-based screening assay using a *hybrid* yeast/mammalian G-protein coupled receptor and a reporter gene. Sledjiewski does not teach or suggest an assay in which yeast cells express a *heterologous* G-protein coupled receptor, a

hybrid Gα protein, or a reporter gene, which elements are required by the cells claimed in the instant invention.

The Examiner's rejection is based on the misconception that the *hybrid* receptors taught by Sledjiewski are the same as the *heterologous* receptors disclosed in the instant application. In fact, there is a critical distinction between a *heterologous* receptor and a *hybrid* receptor. The term "heterologous" receptor, as used in the instant application, refers to a receptor originating from an organism other than the host organism, *i.e.*, a foreign host. Examples of such heterologous receptors are recited in the instant specification and include dopaminergic, muscarinic cholinergic, α-adrenergic, β-adrenergic, opoid, cannabinoid, seratoniergic, and GABAergic receptors, as well as mutants thereof (see page 43, lines 33 to 37 and Table 2 on pages 130 to 146). Such foreign proteins may be engineered for heterologous expression in yeast, for example, by genetically manipulating the gene encoding the foreign receptor for expression in yeast. Addition of host sequences, such as yeast promoter sequences, for example, facilitates transcription of the foreign gene or signal sequences to facilitate secretion of the foreign protein (see page 7, line 28 to page 8, line 8; page 44, lines 5-12).

A "hybrid" or "chimeric" protein, on the other hand, refers to a protein which is derived from at least two different parental proteins. A hybrid protein is not identical in sequence to either of the parental proteins, but, rather, borrow features from both parental proteins (see page 27, lines 2 to 7). A hybrid protein does not originate from a foreign organism, but rather, is constructed from portions from at least two different proteins.

The Examiner's comparison of the hybrid receptors of Sledjiewski with the heterologous receptors of the instant application is inconsistent with the disclosure of the instant application, which clearly distinguishes foreign, heterologous proteins from chimeric or "hybrid" proteins. It is also inconsistent with the ordinary usage of the term by the skilled artisan, and is even inconsistent with the manner these terms are used within the cited references (see, for example, Sledjiewski, page 21, col. 1, "Example 5", and throughout; Kang, page 2585, col. 2, paragraph 2, and throughout).

Given this distinction, it is clear that Sledjiewski does <u>not</u> teach or suggest the use of a *heterologous* receptor in the yeast cell-based screening assay. Rather, Sledjiewski exclusively teaches the use of a *hybrid* receptor in its assays. In fact, the only reference made to a heterologous receptor occurs in Example 4 (col, line 64 to col. 20, line 68), where a

heterologous G-protein coupled receptor, the human β2 adrenergic receptor, is expressed in yeast cells for use in ligand-binding studies. However, the yeast cells of Example 4 which comprise a heterologous G-protein coupled receptor lack two essential elements of the claimed invention: (i) a hybrid G protein and (ii) a reporter gene, two required elements of the transformed yeast cells of the claimed invention. Moreover, there is no teaching or suggestion in Sledjiewski, or elsewhere in the art, to add these elements to the Sledjiewski cells. Sledjiewsky does not disclose or even suggest that such cells, comprising heterologous G-protein coupled receptors, be used in a screening assay. Instead, Sledjiewski teaches away from the claimed invention, by teaching that the a hybrid yeast/mammalian receptor, not a heterologous receptor, be used in screening assays.

2. The Teachings of Kang

Kang reports the results of a study of yeast/mammalian hybrid Gα proteins expressed in yeast, in order to dissect the functional domains of Gα subunits. In particular, the Kang study focused exclusively on the interaction of Gα subunit with the Gβγ subunit, by testing the ability of hybrid Gα proteins to substitute for yeast Gα by monitoring the hybrid's ability to complement the growth defect due to *scg1* null mutations. Yeast cells with the *scg1* null mutation lack the Gα subunit and are therefore defective in ligand-induced signal transduction (*i.e.* pheromone-induced signaling), resulting in constitutive activation of pheromone response pathway. In this assay, the effect of the Gα hybrids expression on signal transduction activity only downstream of the receptor is detected. As shown in Table 2, this study revealed that all of the hybrid Gα proteins were capable of inhibiting activation of pheromone response pathway, indicating a productive interaction between the hybrid Gα with the βγ subunit.

D. There Is No Suggestion to Combine Kang and Sledjiewski, Either in the References Themselves or in the General Knowledge of the Art

Neither Kang nor Sledjiewski, either alone or taken together, suggest the invention, or provide a motivation to one of skill in the art, at the time of the invention, to carry out the claimed invention with a reasonable expectation of success.

The Examiner asserts, however, that it would be obvious to one of skill in the art to use the hybrid Gα proteins of Kang in the assay instead of the hybrid G-protein coupled

receptors used in the Sledjiewski '746 patent. According to the Examiner, the motivation to do so is provided by Kang. The Examiner asserts that "Kang stated that portions of mammalian Gα proteins which bind to mammalian receptors but do not interact with βγ subunits could be made to do so by expressing them as hybrid proteins containing yeast sequences" (Office Action, paper no. 18, page 4, lines 1 to 5). The Examiner refers to Table 2 for this putative suggestion.

There is no such suggestion in Table 2 or elsewhere in Kang. The only problem Kang addresses is how Gα interacts with Gβγ. Table 2 reports the results of three assays used to test heterologous and hybrid Gα proteins. All three assays test the ability of Gα hybrids to interact with the Gβδ subunits and transduce signal downstream of the receptor (see page 2585, final paragraph to page 2587, last paragraph). In order to be useful in the cell-based assays of Sledjiewski, the hybrid Gα proteins must be capable of *both* receiving a signal via an effective ligand-receptor interaction *and* effecting downstream signal transduction. However, the hybrids were never tested for their ability to couple to mammalian G protein coupled receptors. It can hardly be argued that Kang taught or suggested the use these hybrids in screening assays when Kang did not even address the question of the ability of the hybrid proteins to bind the cognate mammalian receptor, the most important activity required for a cell-based ligand screening assays. Moreover, even if one had conceived of using Gα hybrids in cell-based screening assays, which is suggested by neither Kang nor Sledjiewski, Kang only provided *half* the solution.

The only experiments in Kang which addressed how the Gα hybrids interact with the receptor, *i.e.*, upstream signaling from the ligand-bound pheromone receptor, are the mating assays. All of the hybrid Gα proteins were sterile, indicating failure of the hybrids to interact with the receptor (Kang, page 2586, second column). Thus, the Kang hybrid Gα proteins are able to interact with the downstream component of the pheromone response pathway but were unable to interact with the pheromone receptor to elicit activation of the pathway in response to pheromone (Kang, paragraph bridging pages 2586 to 2587).

The only experiment in Kang which addressed the possibility of any hybrid with such dual activity, *i.e.*, ability to bind both receptor and Gβγ, in fact, failed. This experiment is reported on page 2588, col. 2, last complete paragraph:

> Because our results suggest that Gαs can bind to yeast βγ, we speculated that the αs-Scg1 hybrid (Fig.2) might be able to interact with both βγ and the pheromone receptors and thus allow

> pheromone response and mating. Instead, expression of this hybrid protein at a level similar to the levels of the functional constructs failed to produce a detectable phenotype. No definitive conclusion can be made from these negative results, although the lack of function of this hybrid protein suggests that its structure may be abnormal.

Thus, even a Gα hybrid containing a yeast portion capable of binding receptor (Scg1) and a mammalian portion capable of binding the Gβγ subunit of yeast, which was predicted to be capable of interacting with both the yeast pheromone receptor and the Gβγ subunit, failed to demonstrate ligand-mediated signal transduction.

Instead of providing motivation, Kang's failure to identify a single Gα hybrid that can productively interact with both the receptor and the Gβγ subunit, would discourage the skilled artisan from using such Gα hybrids in screening assays. The skilled artisan, at the time of the instant invention, would had very little reason to expect success at achieving the claimed invention.

The Examiner, however, contends that Applicants have: (a) mischaracterized the experiments of Kang; (b) made a false comparison between the hybrids of Kang and the instant hybrids; and (c) misunderstood the meaning of "phenotype" and/or misread the Kang paper. Applicants respectfully disagree for the following reasons.

First, with respect to (a), Applicants do not mischaracterize the Kang experiments. Applicants agree with the Examiner that Kang demonstrates: 1) that the Gα subunit hybrids are able to overcome the *scg1* growth arrest phenotype by interacting with the yeast Gβγ subunit, thereby triggering downstream effectors and reversing the *scg1* growth arrest phenotype; and 2) the Gα subunit hybrids are not able to interact with the yeast pheromone receptors. However, the Examiner's statement, "It is the yeast Gβγ subunit and not the Gα subunit that is responsible for signal transduction; this is in contrast to most animal systems wherein the Gα subunit couples to downstream effectors" is not entirely correct. Kang establishes that <u>both</u> the Gα subunit <u>and</u> the Gβγ subunit are responsible for signal transduction in the pheromone response system. While the Gβγ subunit is responsible for downstream signal transduction, the Gα subunit is pivotally involved in signal transduction by binding to the Gβγ subunit in the absence of pheromone, and releasing from the Gβγ subunit in response to ligand binding to the receptor (see DISCUSSION, especially the second paragraph). The downstream effector phenotype, *i.e*, growth arrest, is only <u>one</u> of the

elements required for the cells useful for the drug screening assays of the claimed invention. The cells of the assay must be capable of both receiving a signal via an effective ligand-receptor interaction and effecting downstream signal transduction. As noted above, Kang discloses a Gα hybrid capable of the latter activity, but not the former. Thus, while Applicants agree that the skilled artisan would appreciate that the Kang hybrids are capable of binding Gβγ subunit, the skilled artisan would have not have been able to construct Gα hybrids capable of interacting with a G-protein coupled receptor with a reasonable expectation of success. Thus, Kang provides no motivation to use such hybrids in the cell-based assays of Sledjiewski.

Regarding (b), Applicants do not draw a false comparison between the Kang hybrids and the hybrids of the claimed invention. Applicants agree that Kang was not testing for an interaction between the hybrids and heterologous mammalian receptors and that only yeast pheromone receptors were present in these assays. As the Examiner correctly points out, this is an apples and oranges distinction. The point is, though, that Kang never addressed whether his hybrids interacted with any receptor, either yeast or mammalian, or even suggested the possibility, because Kang was only interested in studying the interaction between the Gα and Gβγ subunits. In fact, prior to the present invention, it was not considered likely that a hybrid Gα protein would be capable of interacting with both a heterologous receptor and a yeast Gβδ subunit, thereby capable of both the downstream and upstream signaling required for the yeast cell-based assays of the invention.

With regard to (c), Applicants agree that complementation of a growth arrest phenotype by the *scg1* null mutant was successfully measured by Kang. However, while this is one phenotypic activity of the Ga hybrid, it is not the only activity required for successful use in the cell-based assays of Sledjiewski. As discussed above, ligand-receptor signal transduction is also required, which, in turn, requires productive Gα subunit hybrid - receptor interactions. Kang's failure to demonstrate such receptor binding activity would lead the skilled artisan away from attempting to use them, with any expectation of success, in such assays.

E. Kang Does Not Cure the Deficiencies of Sledjiewski

Even if the references were combined, the claimed invention would not be achieved. The combination of the cited references does not achieve the claimed invention because: (1)

Sledjiewski does not teach or suggest yeast cells comprising a heterologous G protein-coupled receptor gene and either a hybrid Gα protein or a reporter gene; and (2) the secondary reference Kang does not teach or suggest the use of hybrid Gα proteins in screening assays. Without the knowledge provided by the instant invention that a hybrid Gα protein can be designed and constructed to interact with both a heterologous receptor and a Gβγ subunit, the skilled artisan would not consider producing a yeast cell containing a hybrid Gα protein, heterologous G- protein-coupled receptor gene, and a reporter gene, with a reasonable expectation of success.

In summary, neither Sledziewski nor Kang, alone or taken together, describe a cell comprising a heterologous G protein-coupled receptor gene and a hybrid Gα protein, as required by the claimed invention. While Sledziewski describes a yeast cell transformed with a heterologous receptor, Skedjiewski does not disclose or suggest that such cells contain either a reporter gene or a hybrid Gα protein. In fact, Sledziewski teaches away from such a cell, by providing an alternative method for yeast cell-based screening assays which use *hybrid* G-protein coupled receptors. While Kang discloses a transformed yeast cell containing a yeast hybrid Gα protein, Kang does not disclose or suggest that such hybrid Gα proteins can bind a receptor, or that they could be used in screening assays, such as the assays of the present invention.

Moreover, neither reference, nor the general knowledge at the time of the invention, provided one of one of skill in the art at the time of the instant invention a motivation to combine the references in such a way that would yield the claimed invention. Without the teachings of the instant invention that a hybrid Gα protein is capable of interacting with both the receptor and the Gβγ subunit, one of skilled in the art would not have thought of using such hybrid proteins in a cell-based screening assay. It is only with impermissible hindsight that the Examiner has combined these references to purportedly achieve the claimed invention. One of skill in the art would not have been motivated to combine these references, without the disclosure of the claimed invention, with any reasonable expectation of successfully achieving the transformed yeast cells disclosed by the Applicant.

Finally, even when combined, the references do not achieve the claimed invention. The particular combination of the cited references does not achieve the claimed invention because: (1) the primary reference Sledjiewski teaches a yeast cell with a hybrid G protein-

coupled receptor and a reporter gene, but does not teach or suggest the use of *either* a hybrid Gα protein *or* a heterologous G protein-coupled receptor gene in the disclosed assays; and (2) the secondary reference Kang does not teach or suggest that hybrid Gα proteins could be made to bind mammalian receptors and yeast βγ subunits.

In view of the foregoing, the art relied on by the Examiner does not render obvious the method of the claimed invention. Applicants therefore request withdrawal of the rejection under 35 U.S.C. §103.

CONCLUSIONS

Applicants respectfully request remarks be made of record in the file history of the instant application. Applicants believe that the remarks made herein now place the pending claims in condition for allowance. Applicants hereby request an interview with the Examiner should the above remarks require further discussion. The Examiner is invited to contact the undersigned with any questions concerning the foregoing.

Respectfully submitted,

Date: June 14, 2002

Paul J. Zegger 33,821

Paul J. Zegger (Reg. No.)

By: Eileen E. Falvey 46,097

Eileen E. Falvey (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosures

EXHIBIT A

PENDING CLAIMS
Application No.: 09/286,166
Atty. Docket No.: 11072-009-999
(as amended under 37 C.F.R. §1.116 on April 14, 2002)

WHAT IS CLAIMED IS:

43. A transformed yeast cell comprising a reporter gene under control of a pheromone-responsive promoter, a heterologous G protein-coupled receptor gene, each said gene being under the control of a separate promoter, a mutation in a SCG1/GPA1 gene, and a hybrid Gα protein.

44. The hybrid Gα protein of claim 43 comprising yeast Gα protein sequences and heterologous Gα protein sequences.

45. The yeast cell of claim 43 further comprising a gene mutation causing increased sensitivity to receptor activation selected from the group consisting of sst2, svg1, ste2, and ste3.

46. The yeast cell of claim 45 further comprising a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

47. The yeast cell of claim 43 wherein the reporter gene is selected from the group consisting of HIS3, URA3, LYS2, CAN1, and Lacz, and the pheromone-responsive promoter is FUS1.

48. The yeast cell of claim 47 further comprising a mutation at a FAR1 gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

49. The yeast cell of claim 47 further comprising a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

50. The yeast cell of claim 43 further comprising a heterologous Gα subunit.

51. The heterologous G protein coupled receptor gene of claims 43 which encodes a receptor selected from the group consisting of a β.2 adrenergic receptor, an α.2- adrenergic receptor, a 5HT-1A receptor, a muscarinic acetylcholine receptor, a growth hormone releasing factor receptor and a somatostatin receptor.

52. The yeast cell of claim 50 further comprising a gene mutation causing increased sensitivity to receptor activation selected from the group consisting of sst2, svg1, ste2, and ste3.

53. The yeast cell of claim 52 further comprising a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

54. The yeast cell of claim 43 and 50 wherein the reporter gene is selected from the group consisting of HIS3, URA3, LYS2, CAN1, and Lacz, and the pheromone-responsive promoter is FUS1.

55. The yeast cell of claim 54 further comprising a mutation at a FAR1 gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

56. The yeast cell of claim 54 further comprising a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

57. The yeast cell of claim 43, 44, 45, or 50 further comprising a heterologous Gα subunit.

58. The heterologous G protein coupled receptor gene of claims 43, 44, 45, or 50 which encodes a receptor selected from the group consisting of a β2 adrenergic receptor, an α2-adrenergic receptor , a 5HT-1A receptor, a muscarinic acetylcholine receptor, a growth hormone releasing factor receptor and a somatostatin receptor.